

**REMARKS**

In response to the final Office action dated January 12, 2010, please consider the following remarks. For reasons provided below, the remarks herein that are different than those earlier presented have been considered unnecessary to support patentability of the claims, which is why they were not earlier presented. Yet, the Applicants urge that these remarks facilitate prosecution of this application and, as such, entry thereof is respectfully requested.

**I. SUMMARY**

As a preliminary matter, the Applicants note that the claims relate, among other things, to the unexpected result that adjuvants comprising iscom particles (i.e. iscoms including subunit antigens or iscom-matrix) can be used together with live attenuated micro-organism vaccines. One of ordinary skill would not have expected these results in view of expected (i) direct physical damage of the live micro-organism upon mixing with saponin-containing iscom particles, (ii) immediate killing at the site of injection by cells and innate mechanisms triggered by the adjuvant effects of the iscom particles, and (iii) killing or replication-inhibition of micro-organisms by proinflammatory/inflammatory mechanisms stimulated by the adjuvant effects of the iscom adjuvant. In this regard, the Examiner's attention is particularly directed to section III-1 below, which specifically addresses a concern raised by the Examiner during the interview of June 8, 2010, regarding teachings of the Morein reference, U.S. Pat. No. 5,679,354, with respect to the issue of lack of reasonable expectation of success.

## II. FORMAL MATTERS

### A. Record of Interview

Applicants' counsel thanks the Examiner for granting a telephone interview on June 8, 2010. The interview was focused on the Applicants' argument, as previously presented, that Van Woensel, in combination with Morein, would not have provided a reasonable expectation of success with regard to the claimed methods or compositions because iscom particles were known to trigger multiple inflammatory responses in a host, inflammatory responses were known to be potentially deleterious to a host and to a live micro-organism therein, and the bases of these responses with regard to iscoms were not understood, and thus the extent and effect of these responses upon administration of an iscom particle and a live micro-organism in a single composition would not have been predictable to any degree. An outline for the interview is attached as Appendix A. It is believed that the Remarks, Declaration, and other evidence submitted herewith address corresponding instructions of the Examiner.

### B. Showing of Good and Sufficient Reasons for Entry of Affidavit or Other Evidence

In response to the final Office action dated January 12, 2010, the Applicants request that the Examiner consider and enter the substantive declaration and other evidence submitted herewith based on the following good and sufficient reasons as to why the declaration and other evidence are necessary and were not earlier presented.

As explained in detail in the remarks below, the Applicants urge that the declaration and other evidence are necessary to facilitate prosecution of this application because arguments and assertions that the Examiner has made for the first time in the above-noted final Office action or

the above-noted interview and upon which the Examiner has maintained all of the rejections (1) do not distinguish between innate immunity, innate induced responses, and the adaptive immune response despite the fundamentally different and in some contexts contradictory roles that each plays in determining whether vaccination with a live micro-organism will result in development of long-lived specific immunity, (2) do not account for the complex role that innate immunity, and inflammation mediated thereby, play in determining whether vaccination with a live micro-organism results in development of a subclinical infection, thus enabling development of long-lived specific immunity based on the adaptive immune response, or instead results in rapid killing of the live micro-organism, thus preventing development of long-lived specific immunity, and/or (3) do not account for the degree to which the details of innate immunity that are pertinent in this regard were poorly understood and highly unpredictable. In this regard, the declaration and other evidence provide basic information about how long-lived specific immunity is achieved by use of live vaccines, including (i) the distinct roles that innate immunity, innate induced responses, and the adaptive immune response play in establishment of long-lived specific immunity, (ii) that innate immunity, and inflammation mediated thereby, play a complex role in determining whether or not vaccination with a live micro-organism will result in long-lived specific immunity, and (iii) that pertinent details of innate immunity were poorly understood and were unpredictable. The declaration and other evidence are thus necessary to facilitate prosecution.

The declaration and other evidence were not earlier presented because, as noted above, the specific arguments, assertions, and concerns of the Examiner that the declaration and other evidence address were raised by the Examiner for the first time in the above-noted final Office action or the above-noted interview. Moreover, the previous Office actions in this case did not

provide a basis to expect that the Examiner's arguments, assertions, and concerns would not distinguish between innate immunity, innate induced responses, and the adaptive immune response or account for the complex role that innate immunity plays or the degree to which the details of innate immunity were poorly understood and highly unpredictable.

Accordingly, entry of the declaration and other evidence submitted herewith is respectfully urged.

C. Other Formal Matters

Applicants continue to acknowledge that the Examiner has withdrawn the species elections with regard to Fraction A and Fraction C of Quillaja Saponaria Molina and that claims 3, 11, 16, 17, and 19 are withdrawn. Applicants note again that claims 3 and 11 depend from claims 1 and 9, respectively. Accordingly, on allowance of claims 1 and 9, rejoinder and allowance of claims 3 and 11 is respectfully requested pursuant to the Office's rejoinder procedure. MPEP § 821.04.

Applicants acknowledge that the Examiner has withdrawn the prior objection to prior claim 26, where the objection had been based on the informality that the claim apparently would have more clearly described the claimed invention by indicating that the composition provides for enhanced immunogenicity of the live micro-organism in a host.

No claims have been amended herein.

III. REJECTION OF CLAIMS 1, 2, 4, 9, 10, 12, 15, 18, AND 24-26 UNDER 35 U.S.C. §

103(A) OVER VAN WOENSEL IN COMBINATION WITH MOREIN

The Examiner has maintained the prior rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 under 35 U.S.C. § 103(a) as being unpatentable over Van Woensel et al. (U.S. Pat. No. 5,925,359) in combination with the teachings of Morein (U.S. Pat. No. 5,679,354). Respectfully, for at least the reasons previously presented, and additionally as explained below in a point-by-point analysis that addresses each assertion and argument raised by the Examiner during the interview of June 8, 2010 and in the final Office action dated January 12, 2010, Van Woensel, in combination with Morein, does not make obvious a method of preparing an antigenic composition, comprising mixing an iscom particle and at least one live micro-organism, wherein the iscom particle is used as an adjuvant, as claimed in claim 1 and the claims depending therefrom, or a composition comprising at least one iscom particle and at least one living micro-organism, as claimed in claim 9 and the claims depending therefrom, respectively.

1. The Examiner expressed a concern during the interview that a person of ordinary skill could have had a reasonable expectation of success with regard to use of the claimed compositions and methods because the above-mentioned '354 Morein patent indicates that “[n]o side effects in the form of local reactions were noted” in host mice following immunization with envelope protein from influenza virus in the form of iscom complex particles or with iscom matrix particles, col. 8, lines 27-56, and that a person of ordinary skill could have understood the absence of such side effects to imply that live micro-organisms could likely survive long enough in the hosts to stimulate long-lived specific immunity.

Respectfully, in addition to the reasons previously presented in the Amendment dated November 6, 2009, as explained below and as supported by the Declaration of Morein, paras. 4-8, submitted herewith, a person of ordinary skill would not have had a reasonable expectation of success with regard to use of the claimed compositions and methods, even taking into account the above-noted disclosure of the Morein '354 patent, because iscom particles administered at dosages similar to those reported in the Morein '354 patent were known to trigger intense inflammatory responses in a host and to be cleared rapidly from sites of injection, side effects in the form of local reactions were known to be most common with adjuvants that are not cleared rapidly from sites of injection, not with adjuvants, such as iscom particles, that are cleared rapidly, and thus an absence of side effects in the form of local reactions would have been understood to reflect rapid clearance of iscom particles from sites of injection, not a lack of intensity of iscom-triggered inflammatory responses.

As a preliminary matter, a person of ordinary skill would have understood the term side effects in the form of local reactions, as used in the Morein '354 patent, to mean undesirable or toxic side effects such as granulomas in particular, not inflammatory responses or inflammation in general, because the only specific side effects that the Morein '354 patent discusses are the undesirable side effects associated with conventional adjuvants, i.e. granulomas at the injection site associated with use of Freund's complete adjuvant or aluminium hydroxide, col. 1, lines 26-32, the Morein '354 patent suggests that the toxic side effects caused by adjuvants when used conventionally can be lowered or avoided when the adjuvants are presented in multimeric form, by analogy with saponins in iscom particles, col. 2, lines 17-24, and the Morein '354 patent nowhere discusses inflammatory responses or inflammation in general.

The fact that iscom particles were known to trigger intense inflammatory responses in a host at dosages similar to those reported in the Morein '354 patent is shown, for example, in a reference to Smith, 162 Journal of Immunology 5536, 5536-37 (1999) (hereinafter "Smith I"), which is already of record in this case and which discloses that intraperitoneal injection, in mice, of iscoms at a dosage equivalent to 0.5  $\mu$ g of Quil A and 5  $\mu$ g of OVA protein "induced intense local inflammation, with early recruitment of neutrophils and mast cells followed by macrophages, dendritic cells, and lymphocytes," and that "[m]any of the recruited cells had phenotypic evidence of activation and secreted a number of inflammatory mediators, including nitric oxide, reactive oxygen intermediates, IL-1, IL-6, IL-12, and IFN- $\gamma$ ." For comparison, the dosages reported in the Morein '354 patent were 0.1  $\mu$ g of iscom matrix or 5  $\mu$ g of iscom including antigen prepared according to EPC 83850273.0. Morein '354 patent, col. 8, lines 37-42. The fact that iscom particles were known to trigger intense inflammatory responses is also shown, for example, in references to Morein, 19 Methods 94, 95-96 (1999), and to Smith, 76 Immunology & Cell Biology 263, 266-67 (1998), which are also submitted herewith.

The fact that iscom particles were known to be cleared rapidly from sites of injection is shown for example in a reference to Sjölander, 15 Vaccine 1030, 1031-32, 1035 (1997) (hereinafter "Sjölander I"), which is submitted herewith. Specifically, Sjölander I disclosed that subcutaneous administration of radioactive influenza virus iscoms (i.e. iscoms including solubilized influenza protein) in mice at dosages equivalent to 3  $\mu$ g of Quillaja saponins and 3  $\mu$ g of influenza protein was followed by rapid (< 3 hours) clearance and organ distribution of the influenza virus iscoms, with iscoms being distributed particularly to draining lymph nodes. Sjölander I, pp. 1031-32, 1035. Sjölander I indicates that these results confirm previous results

regarding intraperitoneal immunization and suggest that retention of antigen at the injection site is not a feature of the immune potentiating properties of iscoms. Sjölander I, p. 1035.

The fact that side effects in the form of local reactions were known to be most common with adjuvants that are not cleared rapidly from sites of injection is suggested, for example, by the Morein '354 patent, in view of Sjölander I and another reference to Sjölander, 43 Scand. J. Immunol. 164 (1996) (hereinafter "Sjölander II"), which is also submitted herewith. Specifically, as indicated above, the Morein '354 patent discusses the undesirable side effects associated with conventional adjuvants, i.e. granulomas at the injection site associated with use of Freund's complete adjuvant or aluminium hydroxide, col. 1, lines 26-32. Sjölander I disclosed that release of radioactivity from the injection site after subcutaneous administration of <sup>125</sup>I-labeled flu-ag, i.e. radiolabeled influenza antigen, emulsified in Freund's complete adjuvant was slow, resulting in lower total recovery from blood and organs and retention of radioactivity at the site of injection for the whole experimental period. Sjölander I, p. 1032. Sjölander II disclosed that retention of antigen at the site of injection had also been observed for alum. Sjölander II, p. 170. Taken together, these disclosures would have suggested that side effects in the form of local reactions may be caused by retention of adjuvants at sites of rejection, and thus that an absence of iscom-triggered side effects in the form of local reactions likely reflects rapid clearance of iscom particles from sites of injection, not a lack of intensity of iscom-triggered inflammatory responses.

Of note, a person of ordinary skill would have been particularly concerned about the particular inflammatory responses triggered by iscom particles with respect to practice of the claimed compositions and methods because many of these inflammatory responses were known to play important roles in clearing live micro-organisms from a host, i.e. killing the micro-

organisms. Specifically, iscom-triggered recruitment of neutrophils and macrophages to an injection site would have been expected to promote clearing of live micro-organisms from the site and thus from the host because, as indicated by a reference to Janeway, Immunobiology (2001), Chapter 2, pp. 39-40, submitted herewith, neutrophils and macrophages are phagocytic cells that "have a key role in innate immunity because they can recognize, ingest, and destroy many pathogens without the aid of an adaptive immune response." Nitric oxide and reactive oxygen intermediates would have been expected to promote clearing of live micro-organisms because it was known that nitric oxide, hydrogen peroxide, and superoxide anion are directly toxic to bacteria. Janeway, Chapter 2, p. 40. IL-1 and IL-6 would also have been expected to promote clearing of live micro-organisms because it was known that a major effect of both IL-1 and IL-6 is to increase host body temperature, resulting in decreased replication of bacteria or viruses within the host. Janeway, Chapter 2, p. 80. Moreover, the person of ordinary skill would not have expected iscom particles to promote long-lived specific immunity without first triggering intense inflammatory responses, based for example on the disclosure of Smith I, p. 5536 (indicating that iscom particles prime antigen-specific immune responses at least in part by activating IL-12-dependent aspects of the innate immune system), and also the disclosures of Behboudi, 50 Scand. J. Immunol. 371, 372 (1999) (indicating that the innate immune response, as defined by the production of proinflammatory cytokines, has an important role in the induction of antigen-specific cell-mediated responses by Quillaja saponins), Sjölander, 177 Cellular Immunology 69, 73-75 (1997), Mooij, 78 Journal of Virology 3333, 3335 (2004), and Pyle, 7 Vaccine 465, 470-471 (1989), which are submitted herewith.

Also of note, a person of ordinary skill would also have been particularly concerned about the rapid onset and intensity of iscom-mediated inflammatory responses because research

had suggested that a strong early immune response, e.g. intense inflammatory responses, to a live vaccine may result in a reduced adaptive immune response to the live vaccine. Specifically, a reference to Marshall, 69 Infection & Immunity 6676, 6676, 6678-79 (2001), which is submitted herewith, disclosed that administration, to mice, of recombinant clones of bacillus Calmette-Guérin (“BCG”) engineered to express a natural antagonist of TGF- $\beta$ , an endogenous immunosuppressive cytokine, resulted in a significant reduction in growth of the recombinant BCG in comparison to control BCG in a mouse model and also resulted in “an increase in the production of IFN- $\gamma$  by splenocytes challenged during the acute stage of infection but with diminished recall response assessed after 13 weeks.” Marshall indicated that “[a] possible explanation for this result is that the rapid clearance,” i.e. killing, “of the LAP-BCG constructs,” i.e. the recombinant BCG engineered to express the natural antagonist of TGF- $\beta$ , “has a detrimental effect on the establishment of a long-term memory response.” Marshall, p. 6679. For reference, Marshall had hypothesized that expression of the antagonist of TGF- $\beta$  “would result in reduction in TGF- $\beta$  activity, augmenting the protective immune response of the host and reducing local inflammatory side effects of BCG vaccination.” Marshall, at 6676. In comparison, iscom particles were known to rapidly trigger multiple inflammatory responses, e.g. expression of multiple pro-inflammatory and inflammatory cytokines, as disclosed for example by Smith I, pp. 5536, 5543, and thus one of ordinary skill would have expected that iscom particles would have had an effect even more detrimental than the above-noted expression of the antagonist of TGF- $\beta$  on establishment of long-lived specific immunity to a live vaccine administered therewith.

Of further note, the Examiner’s concern regarding the absence of side effects in the form of local reactions indicates that the Examiner’s argument fails to account for the complex role

that innate immunity, and inflammation mediated thereby, play in determining whether or not vaccination with a live micro-organism results in establishment of long-lived specific immunity. For at least this reason, entry of the declaration and other evidence submitted herewith is necessary to facilitate prosecution.

For at least the reasons above, a person of ordinary skill would not have understood an absence of side effects in the form of local reactions in hosts to imply that live micro-organisms could likely survive long enough in the hosts to stimulate long-lived specific immunity. Rather, the person of ordinary skill would have understood the fact that iscom particles are cleared rapidly from sites of injection to explain the absence of such side effects despite intense inflammatory responses induced by iscom particles. Accordingly, for these reasons as well as the reasons previously presented in the Amendment dated November 6, 2009, the person of ordinary skill would not have had a reasonable expectation of success with regard to practicing the claimed compositions or methods, and thus the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

2. Examiner's assertion/argument: "With respect to the arguments presented both in the attorney's remarks and in the Morein declaration . . . it is noted that none of the evidence presented specifically provides any teaching away from the combination of an iscom with a live vaccine. The teachings in the art indicate that such is generally not done, but fails to provide any teaching that specifically criticizes, discredits, or otherwise discourages the combination of an iscom with a live vaccine." Office action, p. 3.

Contrary to the Examiner's assertion above and in addition to the reasons previously presented by the Applicants, the evidence presented previously and submitted herewith specifically teaches away from a method or composition including an iscom particle and a live micro-organism in a single composition because a person of ordinary skill would have reasoned from the evidence that combining an adjuvant in general, and an iscom particle in particular, with a live micro-organism for use as a vaccine would likely have resulted in deleterious effects to the live micro-organism following administration to a host, thereby decreasing the probability that the live micro-organism could establish a subclinical infection as required for development of long-lived specific immunity against the live micro-organism, and thus would have been unlikely to produce the objective of the Applicants' invention, or for that matter any other desirable objective that may have been mentioned by the Examiner.

"What a reference teaches or suggests must be examined in the context of the knowledge, skill, and reasoning ability of a skilled artisan. What a reference teaches a person of ordinary skill is not . . . limited to what is specifically 'mentioned' or 'written' in the reference. Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention."

Syntex (U.S.A.) LLC v. Apotex, Inc., 407 F.3d 1371, 1380 (Fed. Cir. 2005).

The evidence previously presented and/or submitted herewith indicates that (1) the immunostimulatory properties of adjuvants in general, and the proinflammatory properties of iscom particles in particular, result in inflammation in a host, (2) inflammation is directed, among other things, to rapid killing of live micro-organisms within the host prior to establishment of an infection by the live micro-organisms, and (3) establishment of long-lived specific immunity against a live micro-organism of a live vaccine requires replication of the live

micro-organism in the host in a controlled manner to give a subclinical infection stimulating long-lived specific immunity. Moreover, regarding inflammation in particular, it is also well known that susceptible live micro-organisms include attenuated-vaccine micro-organisms.

More specifically, the fact that the immunostimulatory properties of adjuvants in general, and the proinflammatory properties of iscom particles in particular, result in proinflammatory effects encompassing innate immunity and inflammation in a host has been shown previously, in the Amendment dated November 6, 2009, at pp. 17-18, and in the references to H.F. Stills, Jr., 46 ILAR Journal 280, 280 (2005), and Smith I, p. 5536, both of which are cited therein and are of record. Regarding the proinflammatory properties of iscom particles in particular, Smith I discusses a potential role of IL-12 in establishing the proinflammatory cascade associated with injection of iscom particles, p. 5536, and indicates that iscom particles stimulated the production of a wide range of inflammatory mediators, including the pro-inflammatory cytokines IL-1 and IL-6, p. 5543. The fact that inflammation is directed, among other things, to rapid killing of live micro-organisms within the host prior to establishment of an infection by the live micro-organisms is shown, for example, in the Declaration of Morein submitted herewith, para. 10, and in Janeway, Immunobiology (2001), Chapter 1, pp. 1-2, and Janeway, Chapter 2, pp. 37, 41, and 43, which are also submitted herewith. This fact, which in any event is well known in the art, has also been noted previously by the Applicants in the Amendment dated November 6, 2009, p. 18. The fact that establishment of long-lived specific immunity against a live micro-organism of a live vaccine requires replication of the live micro-organism in the host in a controlled manner to give a subclinical infection stimulating long-lived specific immunity is shown, for example, in the above-noted Morein Declaration submitted herewith, at para. 10, and in Janeway, Immunobiology (2001), Chapter 14, p. 583, and Janeway, Immunobiology (2001), Afterward,

pp. 605-06, which are also submitted herewith. This fact is also apparent from evidence already of record in the case. See Morein Declaration dated May 18, 2009, at para. 7; Fohlman Declaration dated June 15, 2009, at para. 8; see also Nobivac Tricat Data Sheet, [http://www.intervet.co.uk/Products\\_Public/Nobivac\\_Tricat/090\\_product\\_Datasheet.asp](http://www.intervet.co.uk/Products_Public/Nobivac_Tricat/090_product_Datasheet.asp), Declaration of Morein dated November 4, 2009, Exhibit A (highlighting the susceptibility of live attenuated viruses to being killed and thus the importance their viability for effective vaccination).

One of ordinary skill would have reasoned from these facts that developments flowing therefrom would have been unlikely to produce the objective of the Applicants' invention. Specifically, one of ordinary skill considering the above-noted facts that the immunostimulatory properties of adjuvants in general, and iscom particles in particular, result in inflammation, including proinflammatory effects, in a host and that inflammation is directed, among other things, to rapid killing of live micro-organisms, including attenuated-vaccine micro-organisms, within the host prior to establishment of an infection by the live micro-organisms, would have reasoned that combining an adjuvant in general, and an iscom particle in particular, with a live micro-organism for use as a vaccine would likely have resulted in deleterious effects to the live micro-organism following administration to a host. One of ordinary skill considering the additional above-noted fact that establishment of long-lived specific immunity against a live micro-organism of a live vaccine requires replication of the live micro-organism in the host in a controlled manner to give a subclinical infection stimulating long-lived specific immunity would have reasoned that the likely deleterious effects of the resulting inflammation on the live micro-organism within the host would have made it unlikely that the live micro-organism could

establish the subclinical infection required for development of long-lived specific immunity against the live micro-organism.

Of note, one of ordinary skill would have reasoned that combining an adjuvant in general, and an iscom particle in particular, with a live micro-organism for use as a vaccine would likely have resulted in deleterious effects to the live micro-organism following administration to a host even if, as the Examiner suggests, iscoms might have been expected to lack the membrane-permeabilizing activities and detergent activities of the saponins included therein. See Office action dated January 12, 2010, p. 4. This is because these deleterious effects on the live micro-organism following administration to the host would have been expected to have been caused by iscom particles by way of inflammation, independent of any membrane-permeabilizing activities or detergent activities associated with saponins incorporated within the iscom particles.

Also of note, the Examiner's assertion that the teachings in the art fail to provide any teaching that specifically criticizes, discredits, or discourages the combination of an iscom with a live vaccine, despite arguments and evidence previously presented by the Applicants, including that "iscom particles were known to trigger multiple inflammatory responses in a host" and that "inflammatory responses were known to be potentially deleterious to a host and to a live micro-organism therein," Amendment dated November 6, 2009, pp. 16-17 (emphasis added), as consistent with the above-noted basic information provided in the declaration and other evidence submitted herewith, indicates that the Examiner's assertion fails to account for the complex role that innate immunity, and inflammation mediated thereby, play in determining whether or not vaccination with a live micro-organism results in establishment of long-lived specific immunity. For at least this additional reason, entry of the declaration and other evidence submitted herewith is necessary to facilitate prosecution.

Taken together, the teachings of the evidence, as explained above, in view of the knowledge, skill, and reasoning ability of a skilled artisan, as also explained above, would have suggested that the developments flowing therefrom would have been unlikely to produce the objective of the Applicants' invention, or any other desirable objective that may have been mentioned by the Examiner. Thus, for at least these additional reasons, the evidence presented teaches away from the combination of an iscom with a live vaccine, and accordingly the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

3. Examiner's assertion/argument: “[W]hile those of ordinary skill in the art may have considered saponins themselves to be inappropriate for use as adjuvants in live vaccines . . . those of ordinary skill in the art would not have expected the same incompatibility between the use of is[c]oms and live vaccines.” Office action, p. 4.

The Examiner's assertion here is not a compelling basis for rejection of the claims because one of ordinary skill would have given Van Woensel no weight with regard to any suggestion that it might otherwise make regarding use of iscom particles with live vaccines independent of whether or not one of ordinary skill would have expected the same incompatibility between the use of saponins with live vaccines. Rather, for reasons previously provided as well as additional reasons below, Van Woensel's express statement that saponins are an example of suitable adjuvants with regard to the live attenuated vaccine disclosed therein are so implausible, in view of the evidence presented, as to cast doubt on any other general or

specific teachings or suggestions that Van Woensel may make with regard to use of adjuvants in general, and iscom particles in particular, with live vaccines.

“The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings must be considered to the extent that they are in analogous arts.” MPEP § 2143.01 (II). In this regard, “[w]here the teachings of two or more prior art references conflict, the examiner must weigh the power of each reference to suggest solutions to one of ordinary skill in the art, considering the degree to which one reference might accurately discredit another.” Id.

As the Applicants have previously pointed out, Van Woensel expressly states the following: “An adjuvant and if desired one or more emulsifiers such as Tween and Span may also be incorporated in the live attenuated vaccine according to the invention. Suitable adjuvants are for example vitamin E acetate solubilisate, aluminium hydroxide, -phosphate or -oxide, (mineral) oil emulsion such as Bayol and Marcol 52, and saponins. Incorporation of the antigens in Iscoms is also a possible way of adjuvation.” Van Woensel, col. 5, lines 13-20 (emphasis added).

As can be seen, to the extent that one of ordinary skill might otherwise have understood Van Woensel to suggest incorporating an adjuvant into the live attenuated vaccine disclosed therein, one of skill would have noted that Van Woensel expressly states that suitable adjuvants are, for example, saponins. One of ordinary skill would also have noted, as Applicants have previously pointed out, that the passages of Van Woensel cited by the Examiner provide no experimental evidence or other support for this statement, or indeed for any teaching or suggestion that the reference might otherwise make with regard to use of adjuvants in general, or specific adjuvants in particular, with a live vaccine. In contrast, for reasons previously provided

by the Applicants, as well as the reasons provided by the Examiner, one of ordinary skill would have understood the evidence presented in the present case to indicate that saponins would be inappropriate for use as adjuvants in live vaccines, e.g. because of their membrane-permeabilizing activities and detergent activities, as pointed out by the Examiner. One of ordinary skill, recognizing that Van Woensel and the evidence presented conflict, and particularly the degree to which they conflict, and that Van Woensel lacks support, would have considered the evidence presented to accurately discredit the Van Woensel reference with regard not just to any teachings or suggestions that Van Woensel might make with regard to use of saponins with a live vaccine, but also any other teachings or suggestions regarding use of adjuvants in general, and specific adjuvants in particular, including iscom particles, with a live vaccine. This is of course because one of ordinary skill, in weighing the power of a reference to suggest solutions, would have considered the implausibility of Van Woensel's statement regarding saponins, coupled with the lack of support for any of Van Woensel's teachings or suggestions regarding adjuvants in general and specific adjuvants in particular, to have cast doubt on the plausibility of any of the teachings or suggestions that Van Woensel might otherwise make regarding use of adjuvants in general and the remaining specific adjuvants in particular, including iscom particles, with live vaccines.

Of note, to the extent that the Examiner might be concerned that one of ordinary skill in the art might somehow have ignored the implausibility of Van Woensel's express statement that suitable adjuvants are, for example, saponins, and might otherwise have looked to Van Woensel with respect to other teachings or suggestions regarding specific adjuvants for use with a live vaccine, one of ordinary skill would have immediately recognized that Van Woensel's additional express statement that vitamin E acetate solubilisate and mineral oil emulsion such as Bayol and

Marcol 52 are suitable adjuvants for use with Van Woensel's live attenuated vaccine are likewise implausible, because one of ordinary skill would have readily recognized that solubilisates and mineral oil emulsions are incompatible with live micro-organisms, as noted in the Morein Declaration submitted herewith, at paras. 15, 17, and because the passages of Van Woensel cited by the Examiner also provide no support regarding these additional specific adjuvants. This of course would have cast further doubt on the plausibility of any of the teachings or suggestions that Van Woensel might otherwise make regarding use of adjuvants in general and the remaining specific adjuvants in particular, including iscom particles, with live vaccines.

Of further note, to the extent that the Examiner might be concerned that one of ordinary skill in the art might somehow have ignored the further implausibility of Van Woensel's express statement that vitamin E acetate solubilisate and mineral oil emulsion such as Bayol and Marcol 52 are suitable adjuvants for use with Van Woensel's live attenuated vaccine, and might otherwise have looked to Van Woensel with respect to other teachings or suggestions regarding specific adjuvants for use with a live vaccine, one of ordinary skill would immediately have recognized that while Van Woensel states with apparent, though implausible, certainty that saponins, vitamin E acetate solubilisate, and mineral oil emulsion such as Bayol and Marcol 52 are "suitable" adjuvants for use with the live attenuated vaccine of Van Woensel, Van Woensel qualifies any suggestion regarding use of iscom particles by stating that incorporation of the antigens in iscoms is a "possible" way of adjuviation. The implausibility of the statements regarding saponins, vitamin E acetate solubilisate, and mineral oil emulsion such as Bayol and Marcol 52, coupled with the qualification of the statement regarding iscoms, would have cast terminal doubt on the plausibility of any of the teachings or suggestions that Van Woensel might

otherwise make regarding use of iscom particles with live vaccines, as noted in the Morein Declaration submitted herewith, at para. 18.

Of still further note, the Examiner's assertion that a person of ordinary skill would not have expected the same incompatibility between the use of the iscoms and live vaccines indicates again that the Examiner's assertion fails to account for the complex role that innate immunity, and inflammation mediated thereby, play in determining whether or not vaccination with a live micro-organism results in long-lived specific immunity. For at least this additional reason, entry of the declaration and other evidence submitted herewith is necessary to facilitate prosecution.

Accordingly, independent of whether one of ordinary skill would have expected the same incompatibility between the use of iscom particles and live vaccines as between saponins and live vaccines, one of ordinary skill would have given Van Woensel no weight with regard to any teaching or suggestion that it might otherwise make regarding use of iscom particles with live vaccines. Thus, for at least these additional reasons, the evidence presented teaches away from the combination of an iscom with a live vaccine, and accordingly the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

4. Examiner's assertion/argument: "The second assertion by the Applicants," that the Morein reference does not contemplate use of an iscom particle with a live micro-organism, "is based upon the assertion in the Morein declaration that, while the reference suggests the combination of a whole virus with an iscom the inventors (including Morein) of that reference did not 'intend' that the iscoms would be used with live vaccines." Office action, pp. 4-5.

The Examiner's argument fails for at least the reason that it fails to address the primary basis of Applicants' previously presented argument that the Morein reference, i.e. the above-mentioned U.S. Pat. No. 5,679,354, would not have taught, suggested, or motivated including an iscom particle and live micro-organism in a single composition, namely that one of ordinary skill in the art would not have interpreted the Morein reference to contemplate use of an iscom particle with a live micro-organism. Applicants' argument in this regard, as previously presented, was based on two sub-arguments. First, Applicants argued that "to the extent that the Morein reference discusses including an iscom particle and a micro-organism in a single composition, Morein refers to a virus in general, not to a live virus in particular," as illustrated by quoting the passage from the Morein reference itself that the Examiner cited in the previous Office action, which does not anywhere include the word "live" and thus which does not include all of the limitations of the claims. Amendment filed November 6, 2009, p. 14. Second, Applicants argued that "there is nothing in the Morein reference to suggest that live viruses were intended or would be useful," because "[a]s indicated above, one of ordinary skill would not have expected methods or compositions including an adjuvant and a live micro-organism in a single composition to have been desirable or useful, and thus, given the absence of a specific teaching about a live virus, would not have understood Morein's disclosure to be applicable to live viruses," and because "one of ordinary skill would have recognized the viruses expressly disclosed in the passage, i.e. picornavirus, adenovirus, and parvovirus, are virulent viruses, and given the absence of a qualification regarding attenuation would have recognized that Morein was necessarily referring to killed virus." Amendment filed November 6, 2009, pp. 14-15 (referring to evidence presented earlier in the amendment and to Example 4 of the specification of the instant application for support) (emphasis added). As can be seen, these arguments

provide the primary basis of Applicants' assertion that the Morein reference would not have taught, suggested, or motivated including an iscom particle and live micro-organism in a single composition. As can also be seen, these arguments refer to the text of the Morein reference and the understanding of one of ordinary skill in the art, not to the Morein Declaration or the intentions of the inventors of the Morein reference, and moreover refer to evidence presented earlier in the Amendment and to Example 4 of the specification of the present application for support, not to the Morein Declaration. Indeed, the only reference that the Applicants made to the Morein Declaration in this regard was that Morein has averred in a declaration in the present case that the inventors of the Morein reference "did not intend that Quillaja saponin and/or iscom matrix/iscom particles would be used with live whole microorganisms," which, of course, while being consistent with the Applicants' argument, is not the primary basis of the argument. Thus, for at least these additional reasons, the evidence presented teaches away from the combination of an iscom with a live vaccine, and accordingly the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

5. Examiner's assertion/argument: Applicants' assertion that the combined teachings of the Van Woensel and Morein references fail to cure the deficiencies of the references individually fails for at least the reasons above. Office action, p. 5.

The Examiner's argument fails for at least the reasons previously presented, as well as for the reasons provided above. Thus, for at least these additional reasons, the evidence presented teaches away from the combination of an iscom with a live vaccine, and accordingly the

Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

6. Examiner's assertion/argument: “[T]he rejection is not solely dependent on the use of iscoms as direct adjuvants for the live vaccines. Rather, Van Woensel teaches the use of iscoms as adjuvants for subunit or inactivated vaccines that may be used in combination with the live viruses. . . . Thus, the combined teachings in the art render obvious the use of iscoms in the same compositions as live virus vaccines, whether as adjuvants for the live virus, or primarily as adjuvants for incorporated non-live antigens (with only secondary activity as an adjuvant for the included live virus).” Office action, p. 5.

Contrary to the Examiner's assertion above and in addition to the reasons previously presented by the Applicants, as well as the reasons above, the combined teachings in the art do not render obvious the use of iscom particles in the same composition as live virus vaccines, whether as adjuvants for the live virus, or primarily as adjuvants for incorporated non-live antigens with only secondary activity as an adjuvant for the included live virus. This is because one of ordinary skill in the art would find Van Woensel to lack credibility with regard to teaching a combination of iscom particles and a live vaccine, whether as an adjuvant for the live virus or other micro-organism as discussed previously and above, or as adjuvants for incorporated non-live antigens. Either way, one of ordinary skill in the art would have expected the use of iscom particles with a live vaccine to raise the same problems as noted previously and above, e.g., one of ordinary skill would have expected the immunostimulatory properties of iscom particles to induce inflammation and thereby to decrease the probability that the live

micro-organism of the live vaccine would be able to establish the subclinical infection necessary for establishment of long-lived specific immunity against the live micro-organism, and the establishment of the long-lived specific immunity against the live micro-organism would have been the only compelling reason for including the micro-organism in a live state in the vaccine. Thus, for at least these additional reasons, the evidence presented teaches away from the combination of an iscom with a live vaccine, and accordingly the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

7. Examiner's assertion/argument: "Applicant's second argument in traversal is that there would have been no reasonable expectation of success in the use of the iscoms as adjuvants for the compositions as claimed in the view of the multiple and potentially deleterious responses that iscoms may induce. The arguments are directed to both potentially negative results in the host to whom the vaccine is to be administered, and to the live vaccine included in the composition. The arguments are not found persuasive." Office action, p. 6.

The Examiner's argument fails for at least the reason that it fails to address an express basis of Applicants' argument with regard to lack of a reasonable expectation of success, namely that the effect of iscom particles on a live micro-organism within a host, i.e. after administration of a composition including iscom particles and a live micro-organism, would not have been predictable to any degree, and thus one of ordinary skill would not have had a reasonable expectation of success with regard to use of iscom particles with a live vaccine to establish long-lived specific immunity against the live micro-organism of the live vaccine. The effect of iscom particles on a live micro-organism within a host would not have been predictable to any degree

for at least the reason, as previously presented and with evidentiary support as provided previously and above, that “iscom particles were known to trigger multiple inflammatory responses in a host, inflammatory responses were known to be potentially deleterious to a host and to a live micro-organism therein, and the bases of these responses with regard to iscoms were not understood and thus the extent and effect of these responses upon administration of an iscom particle and a live micro-organism in a single composition would not have been predictable to any degree.” Amendment dated November 6, 2009, pp. 16-17 (emphasis added). Support for the fact that iscom particles were known to trigger multiple inflammatory responses in a host is already of record. Amendment dated November 6, 2009, p. 17 (citing Smith I, p. 5536). Support for the fact that inflammation can be highly detrimental to a live micro-organism therein, i.e. a live micro-organism within a host, is provided as indicated above, for example in the Declaration of Morein submitted herewith, at para. 10, and in Janeway, Chapter 1, pp. 1-2, and Janeway, Chapter 2, pp. 37, 41, and 43, which are also submitted herewith. Support for the fact that the bases of these responses with regard to iscoms were not understood is also already of record. Amendment dated November 6, 2009, pp. 19-20 (citing Smith I, p 5544-45). Support is also provided, for example, in the Declaration of Morein submitted herewith, at paras. 19-21 and in Janeway, Afterword, p. 608, also submitted herewith. Janeway in particular indicates that details of innate immunity were poorly understood, stating with regard to future directions of research in immunobiology that “[o]ne of the big questions is whether immunologists can figure out a way to really understand innate immunity, given that it is a system in which there is really no specific product to measure,” and that “when one moves from experiments that test the functioning of the adaptive immune system to those that test the innate immune system, one is at a loss for proper controls.” One of ordinary skill, considering the above-noted facts, would have

reasoned that the extent and effect of these responses upon administration of an iscom particle and a live micro-organism in a single composition would not have been predictable to any degree.

The Examiner's arguments do not specifically address Applicants' express argument with regard to lack of predictability with respect to the effect of iscom-triggered inflammatory responses on live micro-organisms within a host, and do not otherwise indicate how the effect on a live micro-organism in a host would have been reasonably predictable. Thus, the Examiner has failed to provide a basis for a conclusion that Applicants' arguments in this regard are unpersuasive.

Of note, the failure of the Examiner's arguments to specifically address Applicants' express argument with regard to lack of a reasonable expectation of success with respect to the effect of iscom-triggered inflammatory responses on a live micro-organism within a host, despite the above-noted arguments and evidence previously presented by the Applicants, as consistent with the above-noted basic information provided in the declaration and other evidence submitted herewith, indicates that the Examiner's arguments fails to account for the lack of reasonable predictability associated with innate immunity and innate induced responses with respect to a live micro-organism within a host. For at least this additional reason, entry of the declaration and other evidence submitted herewith is necessary to facilitate prosecution.

Thus, for at least the additional reasons above, one of ordinary skill would not have had a reasonable expectation of success with regard to practicing the claims, and accordingly the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

8. Examiner's assertion/argument: "With respect to the response of the host to the iscoms, while the art indicates that the iscoms trigger multiple responses, the teachings in the art nowhere indicate that such particles are inappropriate adjuvants due to such responses. Rather it is merely a warning to those in the art that caution should be used when using such adjuvants. However, as similar precautions are required generally when using adjuvants (see e.g. Gupta, teaching the need for balancing adjuvant side effects and benefits for vaccine adjuvanticity), such is not considered a teaching away from the use of such constructs as vaccine adjuvants." Office action, p. 6.

For the reasons indicated above, and regardless of how much caution one of ordinary skill in the art might be have been willing to use when using iscom particles as adjuvants, the evidence cited teaches away from the combination of an iscom with a live vaccine. As a preliminary matter, the Examiner's assertion is directed to the issue of teaching away, not the issue of reasonable expectation of success, and thus Applicants' response here is also directed to the issue of teaching away. Regarding the evidence, the Examiner's assertion refers to the requirement for precautions generally when using adjuvants, but those precautions are in the context of killed vaccines, not live vaccines, and are directed to optimizing results that are specific to use of killed vaccines, not live vaccines. The Examiner provides no indication regarding how or why precautions suitable for use with killed vaccines would be applicable, quantitatively or qualitatively, with respect to live vaccines, e.g. to ensure that iscom-mediated inflammation would not kill the live micro-organisms of administered live vaccines prior to establishment of the corresponding subclinical infection that is required for establishment of long-lived specific immunity by live vaccines.

Of note, the Examiner's assertion that while the art indicates that iscoms trigger multiple responses, that the teachings in the art nowhere indicate that such particles are inappropriate adjuvants due to such responses, despite arguments and evidence previously presented by the Applicants that although iscoms trigger multiple inflammatory responses, only production of IL-12 appears to be of major importance with regard to generating antigen-specific immunity, Amendment dated November 6, 2009, pp. 17-18, indicates that the Examiner's assertions fails to distinguish between innate immunity, innate induced responses, and the adaptive immune response despite the fundamentally different and in some contexts contradictory roles that each plays in determining whether vaccination with a live micro-organism will result in development of long-lived specific immunity. In this regard, Applicants note that Janeway, Afterword, p. 606, specifically warns against making such an error, stating that “[t]he adaptive immune response may be thought of in three phases or developmental stages (not to be confused with the three phases of innate immunity, innate induced responses, and the adaptive immune response described in Chapter 1),” consistent with Applicants' previously presented arguments and evidence, as well as arguments and evidence presented above. For at least this additional reason, entry of the declaration and other evidence submitted herewith is necessary to facilitate prosecution.

Accordingly, the Examiner has provided no basis for asserting that the use of caution would somehow have made it likely to produce the objective of the Applicants' invention, or indeed any other desirable objective, or to otherwise negate a “teaching away.” Thus, for at least these additional reasons, the evidence presented teaches away from the combination of an iscom with a live vaccine, and accordingly the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

9. Examiner's assertion/argument: “[T]he fact that the iscoms may induce a range of responses is also not found to affect the expectation that the iscoms would be suitable adjuvants. Rather, this adjuvant activity merely indicates that iscoms would have been expected to prime the immune system to induce multiple immune responses against the target antigen. The fact that certain extraneous or non-essential responses would also be induced is not a demonstration that the adjuvant activity as a whole would be extraneous.” Office action, p. 6.

The Examiner's argument fails for at least the reasons that it does not take into account the lack of predictability with regard to how the noted priming effect of iscom particles affects a live micro-organism within a host and that it fails to distinguish innate immunity, innate induced responses, and the adaptive immune response despite the above-noted fundamentally different and in some contexts contradictory roles that each plays in determining whether vaccination with a live micro-organism will result in development of long-lived specific immunity.

As stated in the MPEP, “[o]bviousness does not require absolute predictability, however, at least some degree of predictability is required.” MPEP § 2143.02, II. In this regard, “[e]vidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness.” *Id.* For example, “[a]n invention would not be invalid for obviousness if the inventor would have been motivated ‘to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.’” Pharmastem Therapeutics, Inc. v. Viacell, Inc., 491 F.3d 1342, 1364

(Fed. Cir. 2007) (stating an exemplary basis for finding a lack of a reasonable expectation of success, post-KSR) (emphasis added).

As indicated above, the evidence indicates that establishment of long-lived specific immunity against a live micro-organism requires that the live micro-organism establish a subclinical infection, which itself requires, among other things, that the live micro-organism survive inflammatory responses. As previously noted by the Applicants, it was known in the art that iscom particles trigger multiple inflammatory responses in a host, and that many of the inflammatory responses are extraneous with regard to establishment of long-lived specific immunity based on being nonessential for the immunogenicity of iscom particles *in vivo*.

Amendment dated November 6, 2009, pp. 17-18. As also previously noted by the Applicants, “[i]t was of course also known that inflammation can be highly detrimental to a host and to a live micro-organism therein, for example because inflammation can cause pain to the host and because inflammation is in part aimed at removing from the host an injurious stimuli such as the live micro-organism” and indeed that “attenuated micro-organisms such as micro-organisms included in a live vaccine would be expected to be particularly susceptible to inflammation.”

Amendment dated November 6, 2009, p. 18 (emphasis added). As previously argued by the Applicants, one of ordinary skill would not have been able to reasonably predict the effect of iscom particles and live micro-organisms in a host on the extent of production of an exemplary cytokine, IL-12, let alone the effect of the resulting IL-12 production on the host and live micro-organisms *therein*. Amendment dated November 6, 2009, pp. 19-22. Moreover, as also previously argued by the Applicants, the lack of predictability would have been compounded upon consideration of the fact that iscom particles were known to induce multiple additional and potentially deleterious inflammatory responses, the bases of which were not understood.

Amendment dated November 6, 2009, p. 22. As indicated above, it was well known in the art that establishment of long-lived specific immunity against a live micro-organism of a live vaccine requires that the live micro-organism establish a subclinical infection. In view of these arguments and facts, one of ordinary skill would not have recognized any degree of predictability with regard to the effect of the administration of a composition including an iscom particle and a live micro-organism on the ability of the live micro-organism to establish the subclinical infection necessary to establish long-lived specific immunity. Thus, even if the evidence presented and references cited had provided a motivation to practice the claimed methods and compositions, which they did not, the evidence and references would have provided nothing more than motivation to vary all parameters or try each of numerous possible choices (e.g. exercise caution as suggested by the Examiner) until one possibly arrived at a successful result, because the prior art gave no indication of which parameters were critical and no direction as to which of many possible choices were likely to be successful. Accordingly, one of ordinary skill would not have had a reasonable expectation of success with regard to practice of the claimed methods or compositions.

Of note, with respect to the Examiner's specific assertion that "the fact that certain extraneous or non-essential responses would also be induced is not a demonstration that the adjuvant activity as a whole would be extraneous," Applicants have not argued that adjuvant activity as a whole would be extraneous, but rather Applicants have argued that "[t]he above-noted iscom-mediated non-IL12 inflammatory responses," i.e. inflammatory responses that are extraneous based on being nonessential for immunogenicity, "would have been of particular concern, given their risk of harming the host and the live micro-organism therein, with no expected concomitant benefit in terms of providing specific immunity," Amendment dated

November 6, 2009, pp. 18-19 (emphasis added), with support as provided previously and above.

Accordingly, the Examiner's assertion does not address the specific basis of Applicants' arguments with regard to problems associated with non-IL12 inflammatory responses being extraneous, or the basis of any other argument made by the Applicants.

Also of note, the Examiner's express statements that "the fact that the iscoms may induce a range of responses is also not found to affect the expectation that the iscoms would be suitable adjuvants" and particularly that "[r]ather, this adjuvant activity merely indicates that iscoms would have been expected to prime the immune system to induce multiple immune responses against the target antigen," despite the above-noted arguments and evidence previously presented by the Applicants with regard to the potential deleterious effects and lack of predictability associated with iscom-mediated inflammatory responses on live micro-organisms in a host and thus on development of long-lived specific immunity based on the adaptive immune response thereto, as consistent with the above-noted basic information provided in the declaration and other evidence submitted herewith, again indicates that the Examiner's argument fails to distinguish innate immunity, innate induced responses, and the adaptive immune response. For at least this additional reason, entry of the declaration and other evidence submitted herewith is necessary to facilitate prosecution.

Thus, for at least the additional reasons above, one of ordinary skill would not have had a reasonable expectation of success with regard to practicing the claims, and accordingly the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

10. Examiner's assertion/argument: "With respect to the uncertainty regarding IL-12 responses, regardless of the expectation regarding such responses, those of ordinary skill in the art would have had some expectation that the iscom would provide some benefit as an adjuvant to the compositions suggested by the teachings of the applied references. While the precise effects on IL-12 production may not have been known, this is not essential to a finding that there would have been a reasonable expectation of success in the use of a known adjuvant as an adjuvant in a suggested vaccine composition." Office action, pp. 6-7.

For reasons previously provided as well as those above, the Examiner's argument fails because it fails to account for the fact that establishment of long-lived specific immunity against a live micro-organism of a live vaccine requires that the live micro-organism establish a subclinical infection, an outcome regarding which one of ordinary skill would not have had a reasonable expectation of success with respect to a vaccine including an iscom particle and a live micro-organism. In this regard, the lack of predictability of the effect of an iscom particle and a live micro-organism on production of the exemplary cytokine IL-12, as well as the multiple additional and potentially deleterious inflammatory responses, would have precluded a reasonable expectation of success with regard to whether the live micro-organism would be able to establish the required subclinical infection and thus with regard to whether compositions or methods including an iscom particle and a live micro-organism would have provided a successful result. Thus, for at least the additional reasons above, one of ordinary skill would not have had a reasonable expectation of success with regard to practicing the claims, and accordingly the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

11. Examiner's assertion/argument: "With respect to the potential to harm the live vaccine, it is . . . noted that the negative attributes of saponins relative to live vaccines is not necessarily present with respect to iscoms" and that "if those in the art did fear for the inactivation of the live antigens by the iscoms, it would . . . have been obvious to those in the art to limit such effects (if any) through the combination of the iscoms and viruses immediately prior to use." Office action, p. 7.

Again, for at least the reasons provided above, the Examiner's argument fails because it fails to account for the fact that establishment of long-lived specific immunity against a live micro-organism of a live vaccine requires that the live micro-organism establish a subclinical infection, an outcome regarding which one of ordinary skill would not have had a reasonable expectation of success. In this regard, the establishment of the required subclinical infection would not have been reasonably predictable, whether or not the negative attributes of saponins relative to live vaccines are present with respect to iscom particles and whether or not iscom particles and viruses were combined immediately prior to use. Thus, for at least the additional reasons above, one of ordinary skill would not have had a reasonable expectation of success with regard to practicing the claims, and accordingly the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

12. Examiner's assertion/argument: The Examiner argues that the results presented by the Applicants would not have been unexpected with regard to not decreasing replication of the live

micro-organism and of increasing the antibody titre against the live micro-organism. Office action, pp. 7-8.

Again, for at least the reasons provided previously and above, the Examiner's argument fails because it fails to account for the fact that establishment of long-lived specific immunity against a live micro-organism of a live vaccine requires that the live micro-organism establish a subclinical infection, an outcome regarding which one of ordinary skill would not have had a reasonable expectation of success. Thus, for at least the additional reasons above, one of ordinary skill would not have had a reasonable expectation of success with regard to practicing the claims, and accordingly the Applicants respectfully request that the rejection of claims 1, 2, 4, 9, 10, 12, 15, 18, and 24-26 be withdrawn.

IV. REJECTION OF CLAIMS 5-8, 13, 14, AND 20-23 UNDER 35 U.S.C. § 103(A) OVER VAN WOENSEL AND MOREIN IN VIEW OF COX

The Examiner has maintained the prior rejection of claims 5-8, 13, 14, and 20-23 under 35 U.S.C. § 103(a) as being unpatentable over Van Woensel and Morein as applied above, and further in view of Cox et al. (WO 96/11711). Respectfully, for at least the reasons previously provided by the Applicants, as well as the reasons above, Van Woensel in combination with Morein does not teach, suggest, or motivate a method or composition including an iscom particle and a live micro-organism in a single composition, as claimed, or provide a reasonable expectation of success, and the passages cited in Cox do nothing to cure the defects of Morein and Van Woensel in this regard or to provide a reasonable expectation of success. In this regard, as the Applicants have previously noted, the teachings of Cox asserted by the Examiner are not

directed to including an iscom particle and a live micro-organism in a single composition. Accordingly the Applicants respectfully request that the rejection of claims 5-8, 13, 14, and 20-23 be withdrawn.

V. CITATION OF HAANES AS PERTINENT TO APPLICANTS' DISCLOSURE

For at least the reasons previously provided by the Applicants, as well as the reasons above, Haanes is not pertinent to Applicants' disclosure. For example, for reasons similar to those provided previously and above regarding Van Woensel, Haanes lacks authority with regard to any potential teaching, suggestion, or motivation that it might arguably be understood to make regarding combining adjuvants in general, or iscom particles in particular, with a live vaccine. Moreover, Haanes teaches away from a composition including a live virus and an iscom particle by expressly stating that “[o]ne advantage of live virus-based vaccines, such as the recombinant CHVs of the present invention, is that adjuvants and carriers are not required to produce an efficacious vaccine, and in some cases, the advantages of recombinant CHV vaccines of the present invention would be precluded by the use of some adjuvants,” col. 29, lines 26-33, by providing a list of “suitable adjuvants” that does not specifically include iscom particles, col. 29, lines 36-45, and by nowhere else mentioning iscom particles. For at least these reasons, Haanes is not pertinent to Applicants' disclosure.

VI. REQUEST FOR RECONSIDERATION AND THAT APPLICATION BE ALLOWED

In view of the foregoing, Applicants respectfully request reconsideration, submit that the present application is in a condition for allowance, and request notice to that effect. If it is determined that the application is not in a condition for allowance, the Examiner is invited to

initiate a telephone interview with the undersigned attorney to expedite prosecution of the present application.

If there are any additional fees resulting from this communication, please charge the same to our Deposit Account No. 16-0820, our Order No. ALBI-41848.

Respectfully submitted,  
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Date: June 24, 2010

## APPENDIX A

**From:** **Gregory M. York, Pearne & Gordon LLP**  
**To:** **Examiner Zachariah Lucas**  
**Date:** **June 4, 2010**  
**Re:** **U.S. Appl. No. 10/550,026 – Outline for Interview - Not for Entry Prior to Filing Amendment**

A person of ordinary skill would not have had a reasonable expectation of success regarding the claimed methods or compositions in view, for example, of expected deleterious effects of iscom-triggered inflammation on a live micro-organism of a live vaccine within a host (i.e. the live micro-organism of the vaccine after the vaccine has been administered to the host). Development of long-lasting specific immunity to a live vaccine requires that the live micro-organism survive in the host for a sufficiently long time to establish a subclinical infection. Iscom-triggered inflammatory responses would have precluded a reasonable expectation of success in this regard.

- 1) Previously presented argument: Van Woensel, in combination with Morein, would not have provided a reasonable expectation of success with regard to the claimed methods or compositions because iscom particles were known to trigger multiple inflammatory responses in a host, inflammatory responses were known to be potentially deleterious to a host and to a live micro-organism therein, and the bases of these responses with regard to iscoms were not understood, and thus the extent and effect of these responses upon administration of an iscom particle and a live micro-organism in a single composition would not have been predictable to any degree. Amendment dated Nov. 6, 2009, pp. 16-17.
  - i) Iscom particles trigger multiple inflammatory responses in a host. p. 17.
  - ii) Of these responses, only one, production of IL-12, appears to be of major importance with regard to generating antigen-specific immunity. p. 18.
  - iii) Inflammation can be highly detrimental to a host and to a live micro-organism therein . . . because inflammation is in part aimed at removing from a host an injurious stimuli such as the live micro-organism. p. 18.
  - iv) Iscom-mediated non-IL-12 inflammatory responses would have been of particular concern, given their risk of harming the host and the live micro-organism therein, with no expected benefit in terms of providing specific immunity. p. 19.
- 2) Request for clarification: What is the Examiner's position with respect to our argument?
  - i) The final Office action dated January 12, 2010 addresses the effects of iscoms (1) on hosts per se and (2) on live micro-organisms in a vaccine prior to administration to a host. p. 6.
  - ii) However, the Office action does not specifically address our argument regarding the effect of iscom-triggered inflammation on the live micro-organism after administration to the host.
  - iii) If the Examiner considers the Office action to have adequately addressed our argument, we would argue that the Examiner's position fails to distinguish between innate immunity, innate induced responses, and the adaptive immune response despite the fundamentally different and in some contexts contradictory roles that each plays in determining whether vaccination with a live micro-organism will result in development of long-lasting specific immunity.
- 3) Additional evidence: We plan to submit (1) a substantive declaration of one of the inventors and (2) supporting chapters of an immunology textbook to address the Examiner's concerns.
  - i) The evidence relates to basic information about how long-lasting specific immunity is achieved by use of live vaccines, including the requirement that the live micro-organism survive in the host for a sufficiently long time to establish a subclinical infection, an outcome for which there would not have been a reasonable expectation of success in view of multiple iscom-triggered inflammatory responses.
  - ii) We can discuss potential additional evidence too.
  - iii) We will state our good and sufficient reasons as to why the declaration and other evidence are necessary and were not earlier presented.